

**CONTRACEPTION WITH SUBDERMAL IMPLANTS
RELEASING LEVONORGESTREL**
A clinical and pharmacological study

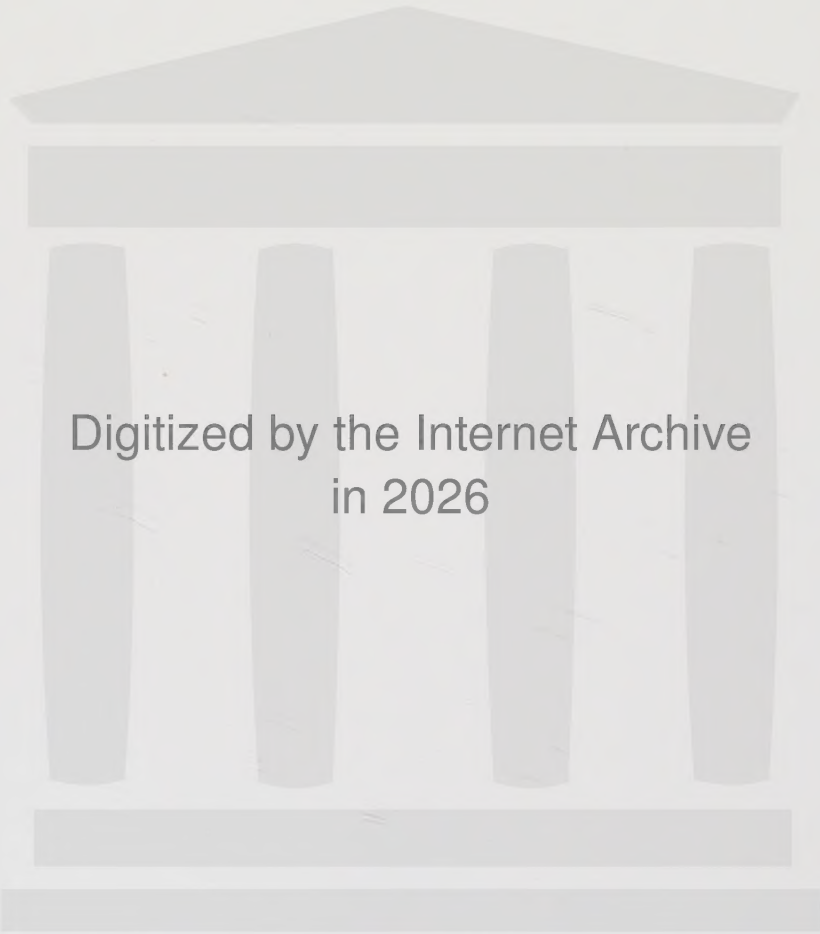
by

Sven-Eric Olsson



UPPSALA UNIVERSITY

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ABSTRACT

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Two methods for release of levonorgestrel from polydimethylsiloxane (Silastic^R) subdermal implants for contraception were studied. The first system consists of six 3 cm long Silastic^R capsules filled with levonorgestrel (NORPLANT^R). The second one consists of two 4 cm long rods made from Silastic^R and levonorgestrel, covered with thin Silastic^R tubing (NORPLANT^R-2). The contraceptive efficacy of NORPLANT^R implants was excellent during the four years of observation. That of NORPLANT^R-2 implants was very good during the first three years, but not acceptable during the fourth year.

Both types of implants were well tolerated and the most common side effect experienced was bleeding disturbances such as irregular bleeding and periods of prolonged bleeding. The frequency of such disturbances decreased considerably after the first year of use.

The plasma levels of levonorgestrel decreased throughout the study, and did not show any statistically significant difference between users of the two types of implants.

The plasma levels of levonorgestrel in women who became pregnant did not differ from those in women who did not become pregnant. Levonorgestrel binds to sex hormone binding globulin (SHBG) with high affinity, and in the bound form is not biologically active. A "free levonorgestrel index" (FLI), i.e. the ratio of plasma level of levonorgestrel to SHBG capacity, was calculated. Women with NORPLANT^R had higher FLI than those with NORPLANT^R-2 and women who became pregnant had lower FLI than those who did not. It is suggested that NORPLANT^R-2 implants have a lower rate of release of levonorgestrel than NORPLANT^R implants.

SHBG capacity, thyroid binding proteins and corticosteroid binding globulin decreased during treatment.

Plasma total testosterone decreased during treatment, whereas free testosterone was unaltered. Thyroid function and plasma cortisol levels did not change during treatment.

Treatment with phenytoin decreased the contraceptive effect.

In a group of regularly menstruating women who had used NORPLANT^R-2 implants for more than three years, 40% showed anovulation, 20% luteinization of unruptured follicles and 40% apparent ovulation.

Key words: Levonorgestrel, subdermal implants, contraception, SHBG, CBG, TBP, androgens, phenytoin, ovary, ultrasound

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CONTRACEPTION WITH SUBDERMAL IMPLANTS RELEASING LEVONORGESTREL

A clinical and pharmacological study

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*To Anna,
Ulrika and Mats*

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ORIGINAL PAPERS

This dissertation is based on the papers listed below, which will be referred to in the following by their Roman numerals:

- I. Olsson S-E, Odling V, Johansson E.D.B, Sivin I: Contraception with NORPLANT^R implants and NORPLANT^R-2 implants (two covered rods). Clinical results from a comparative study in Sweden. Submitted for publication.
- II. Olsson S-E, Odling V, Johansson E.D.B, Nordström M-L: Plasma levels of levonorgestrel and free levonorgestrel index in women using NORPLANT^R implants or two covered rods (NORPLANT^R-2). Submitted for publication.
- III. Sven-Eric Olsson, Viveca Odling, Elov Johansson: Androgen levels in women using NORPLANT^R implants. *Contraception* 34:157 – 167, 1986.
- IV. Olsson S-E, Wide L, Odling V: Aspects of thyroid function during use of NORPLANT^R implants. *Contraception* 34:583 – 587, 1986.
- V. Olsson S-E, Odling V, Hammond GL: Plasma levels of cortisol and corticosteroid binding globulin during use of NORPLANT^R-2 implants. Submitted for publication.
- VI. Viveca Odling and Sven-Eric Olsson: Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with NORPLANT^R implants. *Contraception* 33:257 – 261, 1986.
- VII. Olsson S-E, Bakos O, Lindgren P.G, Odling V, Wide L: Ovarian function during use of subdermal implants releasing low doses of levonorgestrel. Manuscript.

ABSTRACT

Two methods for release of levonorgestrel from polydimethylsiloxane (Silastic[®]) subdermal implants for contraception were studied. The first system consists of six 3 cm long Silastic[®] capsules filled with levonorgestrel (NORPLANT[®]). The second one consists of two 4 cm long rods made from Silastic[®] and levonorgestrel, covered with thin Silastic[®] tubing (NORPLANT[®]-2). The contraceptive efficacy of NORPLANT[®] implants was excellent during the four years of observation. That of NORPLANT[®]-2 implants was very good during the first three years, but not acceptable during the fourth year.

Both types of implants were well tolerated and the most common side effect experienced was bleeding disturbances such as irregular bleeding and periods of prolonged bleeding. The frequency of such disturbances decreased considerably after the first year of use.

The plasma levels of levonorgestrel decreased throughout the study, and did not show any statistically significant difference between users of the two types of implants.

The plasma levels of levonorgestrel in women who became pregnant did not differ from those in women who did not become pregnant. Levonorgestrel binds to sex hormone binding globulin (SHBG) with high affinity, and in the bound form is not biologically active. A "free levonorgestrel index" (FLI), i.e. the ratio of plasma level of levonorgestrel to SHBG capacity, was calculated. Women with NORPLANT[®] had higher FLI than those with NORPLANT[®]-2 and women who became pregnant had lower FLI than those who did not. It is suggested that NORPLANT[®]-2 implants have a lower rate of release of levonorgestrel than NORPLANT[®] implants.

SHBG capacity, thyroid binding proteins and corticosteroid binding globulin decreased during treatment.

Plasma total testosterone decreased during treatment, whereas free testosterone was unaltered. Thyroid function and plasma cortisol levels did not change during treatment.

Treatment with phenytoin decreased the contraceptive effect.

In a group of regularly menstruating women who had used NORPLANT[®]-2 implants for more than three years, 40% showed anovulation, 20% luteinization of unruptured follicles and 40% apparent ovulation.

Key words: Levonorgestrel, subdermal implants, contraception, SHBG, CBG, TBP, androgens, phenytoin, ovary, ultrasound

ABBREVIATIONS

SHBG	=	Sex hormone binding globulin
CBG	=	Corticosteroid binding globulin
TBP	=	Thyroid hormone binding proteins
TBG	=	Thyroid binding globulin
FLI	=	“Free levonorgestrel index”
T ₄	=	Thyroxin
T ₃	=	Triiodothyronin

INTRODUCTION

Progestogen-only contraceptive methods were developed with the aim of avoiding certain side effects and risks associated with the oestrogens in combined oral contraceptive pills. These methods were first thought to affect only the cervical mucus, but later studies have shown that ovulation is affected in more than 50 per cent of the women studied (1, 2, 3). Oral progestogens (i.e. minipills), however, have a limited contraceptive efficacy, which greatly depends on the woman's compliance with the pill regime (4).

In order to increase the contraceptive efficacy without a large increase in dose, non-oral systems for sustained release of progestogens have been developed.

The finding by Folkman and Long (1964) that cardiotrophic drugs, and by Dziuk and Cook (1966) that steroid hormones, could diffuse out of a polydimethylsiloxane (Silastic^R) capsule at a low but fairly constant rate, was first proposed and utilized by Segal and Croxatto for contraception (5, 6, 7). Since this pioneering work, the International Committee for Contraception Research (ICCR) of the Population Council, New York, has continued research in this field with the purpose of providing safe and efficient methods of contraception at a low cost. This work has resulted in the NORPLANT^R implant system, which consists of six Silastic^R capsules for subdermal implantation, which release levonorgestrel at a fairly constant rate for at least 5 years. Except for some initial bleeding disturbances, side effects have been few and the system is readily reversible (8).

Development of NORPLANT^R implants

The initial laboratory studies by Segal and Croxatto (1967) were undertaken in rats and rabbits. They showed that different steroids such as oestradiol, testosterone and progesterone were released from subdermally inserted Silastic^R capsules at different rates (7). The release rate for progesterone was 75 times higher than that of oestradiol. They also found that the hormonal effects could be maintained for more than a year, and that the rate of release increased proportionately to the surface area of the capsules, and decreased with increasing wall thickness.

Medical grade polydimethylsiloxane tubing had previously been used in over 100,000 patients as hydrocephalus drainage tubes without serious foreign body reactions or evidence of neoplasia (9). This vast experience from the use of Silastic^R in humans without side effects was of great importance for the concept that it would

be possible to develop a subdermal implant which could release steroids for contraception.

The first clinical trial of Silastic^R implants was started in Santiago by Croxatto et al. with use of the progestogen chlormadinone acetate (9). The study was discontinued, however, after a short time because of the finding of breast nodules in beagle bitches given this drug (10). This study was too small to establish any evidence of contraceptive efficacy, but it confirmed the principle of a prolonged hormonal effect through this subdermal route with use of Silastic^R capsules.

After 1968, studies with megestrol acetate were initiated in Brazil and Chile. During subsequent years additional studies with megestrol acetate were performed in many other countries with the number of implants used ranging from one to six. The best contraceptive efficacy was obtained with six implants (11, 12, 13, 14).

There were some reports of ectopic pregnancies and adnexal masses among users of continuous low-dose progestogens (15, 16). Also, reports appeared of congenital malformations in fetuses exposed to progestogens in utero (17). These reports on malformations, however, all concerned much higher doses of progestogens given as treatment for threatened abortion.

Against this background, the ICCR of the Population Council decided to concentrate on studying contraceptive implants releasing sufficient doses of steroids to inhibit ovulation, which would thus minimise the above-mentioned risks.

A search for suitable steroids for such an implant method began. In many clinical trials different steroids were examined as candidates for long-acting implant contraception. Among possible agents considered, megestrol acetate, levonorgestrel and norgestrienone were chosen for further testing because of their few side effects, long duration of action and high efficacy (18, 19).

A comparative study of these three steroids, delivered by six Silastic^R capsules, was started in 1975 to determine which one was most suitable for further contraceptive development. Soon after the study had begun megestrol acetate was withdrawn, as it was found that this steroid, also, caused breast nodules in beagle dogs (10). In that study, a comparison group using an IUD (TCu-200) instead of megestrol acetate was recruited. After one year the pregnancy rate for six levonorgestrel capsules was 0.6 per 100 woman-years of use. The corresponding figure for norgestrienone implants was 3.5, and for IUD users 1.6. Menstrual problems more often (12.3%) were a reason for discontinuation of levonorgestrel than of norgestrienone implants (4.3%). The two principal menstrual problems of levonorgestrel users were frequent irregular bleeding and periods of prolonged bleeding. The one-year continuation rate was high, however, ranging from 60 to 91% in different centres (9, 20, 21).

A report by Weiner and Johansson (1976) of the pharmacokinetics and pharmacodynamic effects of six Silastic^R capsules filled with levonorgestrel, showed that the majority of the cycles during the first year of use were anovulatory, and that the plasma levels of levonorgestrel were stable during that year (22).

It was concluded from these studies that the method to be further developed should be six Silastic^R capsules 30 mm long and filled with 36 mg of levonorgestrel. The basis for this decision was the higher contraceptive efficacy and the estimated longer duration of action of levonorgestrel than of norgestrienone implants (9). During one year of use levonorgestrel implants had lost approximately 11% of their initial steroid load, whereas norgestrienone implants had lost approximately 44% (9).

Further phase III clinical studies with six levonorgestrel-containing subdermal Silastic capsules were started in Chile, Brazil, Jamaica, the Dominican Republic, Finland and Denmark. The results of these studies showed that the one-year net pregnancy rate was 0.3 per 100 users (3/992 acceptors). Two of these pregnancies were in fact diagnosed during the first month of use, and these women were most probably already pregnant at the time of entry into the study (23).

Further studies with this levonorgestrel-releasing implant system have confirmed the initially good results, with a failure rate of 4 to 5 per 1,000 continuing users per year, and today more than 70,000 women have used the method. The method has been named NORPLANT^R (NORPLANT^R is the registered trademark of the Population Council for Silastic^R implants containing levonorgestrel) and has to date been approved by regulatory authorities in several countries, for example Finland, Sweden, Indonesia, Thailand and Ecuador.

Development of the covered rods

To reduce the problem of insertion and removal of six implants, a second generation of levonorgestrel-releasing implants with a higher release rate per implant has been developed.

Two such systems have been investigated: the homogeneous rods and the covered rods. The homogeneous rods contain 25%, by weight, of levonorgestrel homogeneously dispersed in Silastic 382 medical grade Elastomer. The covered rods consist of a core rod containing levonorgestrel and Silastic^R Medical Grade Elastomer MDX-4-4092; 50:50, weight:weight. This rod is sealed inside a thin-walled medical grade Silastic^R tubing with Silastic^R Medical Adhesive type A (24).

The release from Silastic^R capsules is of zero order and the release rate is determined by the steady-state Fick's diffusion equation according to which diffusion of a certain drug through the membrane depends only on the thickness of the membrane, given that the concentration of the drug at the internal wall is kept constant (25). To accomplish this, a powdered drug can be loaded at a level far above the solubility of

the drug. As long as the powdered drug is available, the drug concentration at the internal wall will be the saturation concentration of the drug, and zero order release will occur. Through the first 18 months of use, the release of levonorgestrel decreases, and thereafter it remains constant. The initial decrease in release could be due a) to formation of a fibrous capsule around the implant, with a consequent increase in the distance through which the steroid has to diffuse, or b) to very slow diffusion of water into the capsule, so that ultimately the capsule would become filled with water. The solubility of levonorgestrel in water would then become the rate-limiting step, and a constant rate of release would result, but at a lower rate level, as levonorgestrel has a low solubility in water (24).

The release rate from matrix systems, such as the "homogeneous" rods is generally not of zero order but proportional to $t^{-1/2}$, where t is the release time. The rationale for this is that the drug is initially released from the surface layer, and has then only a short distance to travel. At later times drug from deeper levels within the matrix diffuses out and has a greater distance to travel (25).

The homogenous rods are easily broken on removal, a fact which has been considered unacceptable in clinical practise (24).

The covered rods system releases drug at a constant rate which is considerably lower than the initial rate of release from the "homogeneous" rods. With the thin Silastic^R membrane covering, the rate control lies in the membrane itself. As long as the core of 50% drug and 50% silicone rubber provides a constant concentration of drug to the inside surface of the cover, the rate of dissolution in, and diffusion through the covering membrane controls the release (24).

Clinical studies have been performed with four or six covered rods 3 cm long. From these studies the release rate per centimetre has been established. It has also been found that the release is constant throughout the study period, and linearly correlated with time. It has been estimated that two 4 cm long covered rods should have levonorgestrel-release rates similar to those of the six-capsule system. The theoretical lifetime has been calculated to be 8 years. The data for release after three years, however, are not very extensive (26).

The established good performance of NORPLANT^R implants and the promising results with the two covered rods system (NORPLANT^R-2), were the basis for a large clinical trial in which the two implant systems were compared.

AIMS OF THE INVESTIGATION

This investigation was undertaken

1. to study clinical effects in women using NORPLANT[®] implants or two covered rods, to evaluate efficacy, side effects and continuation rate;
2. to compare the blood levels of levonorgestrel in women using NORPLANT[®] implants and in those using two covered rods;
3. to investigate the effects of levonorgestrel on hormone binding proteins such as sex hormone binding globulin (SHBG), thyroid binding proteins (TBP) and corticosteroid binding globulin (CBG), and to study concomitant changes in plasma levels of hormones carried by these proteins; and
4. to study mechanisms behind the contraceptive effect in levonorgestrel releasing implants.

MATERIAL AND METHODS

The studies were performed on several groups of healthy women, of ages between 18 and 40 years. For the comparative studies the women were randomly allocated to groups using either NORPLANT[®] or NORPLANT[®]-2 implants. For efficacy studies, only parous women were recruited.

The implants were manufactured for the Population Council by Leiras Pharmaceuticals, Turku, Finland.

For NORPLANT[®] implants Silastic[®] Medical Grade tubing (inner diameter 1.6 mm) was packed with levonorgestrel crystals and sealed at each end with Silastic Medical Grade adhesive type A. Each capsule was 34 mm long and contained approximately 36 mg of steroid. The steroid-containing length was 30 mm, (Figure 1).

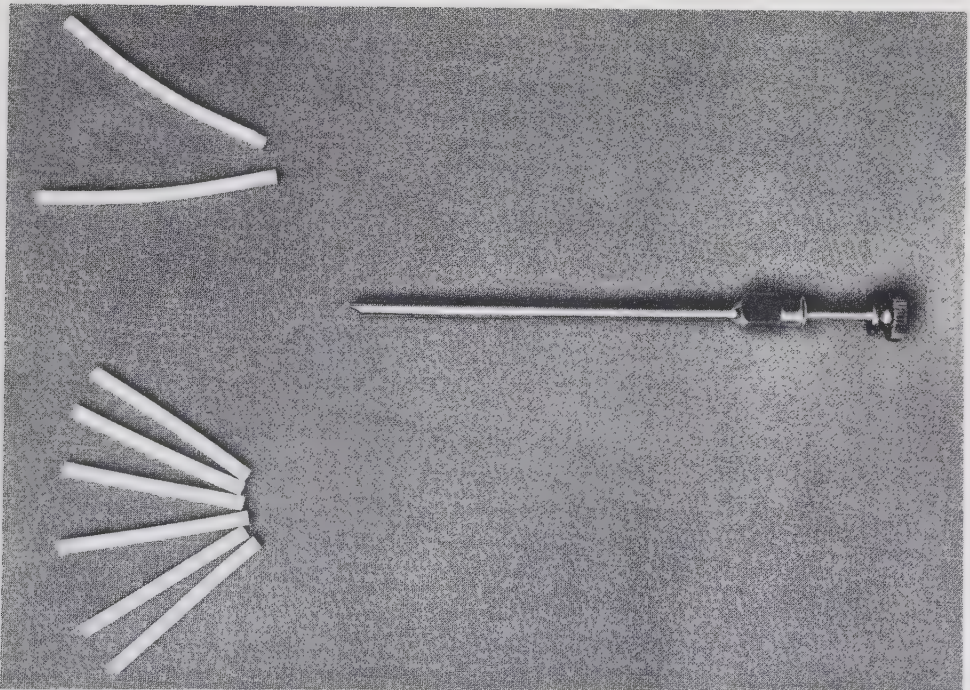


Fig. 1. NORPLANT[®] and NORPLANT[®]-2 implants together with the trocar used for insertions.

For the covered rods (NORPLANT^R-2), the levonorgestrel was dispersed in a cylindrical rod composed of cured Medical Grade Elastomer MDX-4-4092. The rod was then covered with thin Silastic^R tubing and sealed at the ends with Silastic^R Medical Adhesive. The covered rods were 44 mm long and each contained approximately 70 mg of levonorgestrel. The steroid-containing length was 40 mm, (Figure 1).

The outer diameter of both types of implants was 2.4 mm. All implants were sterilized with ethylene oxide.

The release of levonorgestrel from NORPLANT^R implants has been reported to decrease from 60–80 $\mu\text{g}/\text{day}$ during the first year to about 30 μg after 18 months of use. The release of levonorgestrel from the covered rods has been found to be about 50 $\mu\text{g}/\text{day}$. The effective life time of both types of implants has been reported to be at least 5 years (24, 26).

The implants were inserted on one of the five first days of a normal menstruation, or immediately after an abortion. They were placed subdermally in the anterior aspect of the forearm, or in the inner aspect of the upper arm, through a 10-gauge trocar under local anaesthesia. The same insertion technique was used for both types of implants, (Figure 2).

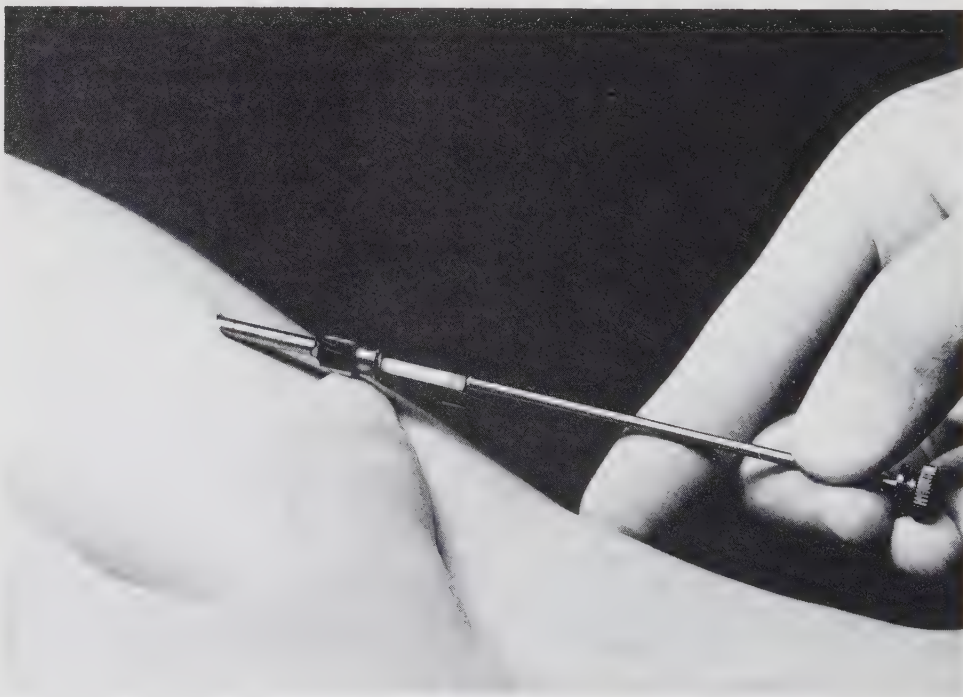


Fig. 2. Insertion of an implant through the trocar.

Removal of the implants was performed under local anaesthesia, using a small forceps and a small scalpel. After a skin incision, the implants were identified, the tissue capsule was opened, and the implants were extracted.

Blood samples for hormone determinations were always drawn from the contralateral arm, as it has been shown by Croxatto et al. that samples from the arm ipsilateral to the implants have higher concentrations of levonorgestrel than those from the contralateral arm (27). The blood was collected in heparinised vials, and the plasma was recovered after centrifugation and kept frozen at -20°C until analysed. Samples for determination of cortisol and testosterone were always drawn at 08.00 AM and 04.00 PM.

For statistical analysis Student's t test for independent or, when appropriate, for dependent samples was used. All values refer to two-tailed tests. As the oestradiol concentrations showed a skewed distribution, the logarithmic values were used for the statistical analysis of oestradiol, and the means for oestradiol levels are given as the geometric means. In one instance the Chi squared test was used. For determination of correlation coefficients, the Pearson least squares method was employed.

For the description and statistical calculations of continuation rates and rates of different events during the comparative study (I), life-table techniques, and sometimes the Pearl Index were used. The life table technique used here has been described by Tietze and Potter. For statistical analysis of events, the log rank Chi squared method and the asymptotic normal distribution were used (28, 29, 30).

The precision in radioimmunological hormone determinations (intraassay coefficient of variation and interassay coefficient of variation) was calculated according to the method of Abraham et al. (31).

The studies were approved by the Drug Regulatory Board of Sweden and the Committee for Medical Ethics of the Faculty of Medicine, Uppsala University.

Hormone determinations

Plasma concentrations of *levonorgestrel* were determined by a specific radioimmunoassay as described previously by Weiner and Johansson (22). Both the antiserum and the tracer (15–16 ^3H -d-norgestrel with a specific activity of 30 to 50 Ci per mM) were obtained from Schering AG, Berlin, Germany. Extraction from plasma was performed with diethyl ether. Because of a small plasma blank, the practical detection limit was 25 pg. No correction was made for procedural losses, nor were the plasma blanks subtracted. The extraction recovery was 89–95%. With the extraction volume of 200 μl , the detection limit was 0.16 nmol/l. For random samples the interassay coefficient of variation (CV) was 10.7% for samples <1.0 nmol/l and 8.0% for those >1.0 nmol/l, and the intraassay CV was 8.7% for samples <1.0

nmol/l and 6.4% for those >1.0 nmol/l. No cross reactions were found between naturally occurring steroids and levonorgestrel.

SHBG capacity was determined according to the method described by Rosner with modifications (32, 33). Plasma was saturated with tritiated dihydrotestosterone (from New England Nuclear, with a specific activity of 50 Ci/mmol) and after incubation was precipitated with ammonium sulphate. After centrifugation, the supernatant was counted in a scintillation counter, and SHBG capacity was calculated as described by Rosner. The normal range for fertile women has been found to be 18–65 nmol/l. The within and between assay CVs were 10% and 17%, respectively.

Total testosterone was measured with a radioimmunoassay, after extraction with diethyl ether, using a commercial kit from Diagnostics Product Corp, Los Angeles, USA. The normal range for fertile women was 0.8–3.0 nmol/l. The within and between assay CVs were found to be 8% and 10%, respectively.

Androstenedione (A4) was measured with a radioimmunoassay, after extraction with diethyl ether, using an antiserum against androstenedione purchased from International CIS, Gif-sur-Yvette, France. The cross reaction with testosterone was 0.4%. The normal range for women 20–40 years of age was 3–11 nmol/l. The within and between assay CVs were found to be 6% and 12%, respectively.

Free testosterone was assayed with a commercial solid-phase radioimmunoassay kit from Diagnostics Products Corp, Los Angeles, USA. The normal range for women 20–40 years of age was 3.0–11.1 pmol/l. The within and between assay CVs were 5% and 6%, respectively.

Thyroxin (T_4) concentrations were measured by a solid phase radioimmunoassay described by Wide (34). Normal values were 67–153 nmol/l.

Triiodothyronine (T_3) was measured by a solid phase radioimmunoassay described by Wide (34). Normal values were 1.2–2.8 nmol/l.

Thyroid stimulating hormone (TSH) was assayed by a radioimmunosorbent technique described by Wide et al. (35). Normal values were <8 mU/l.

T_3 -uptake, as an indicator of the level of thyroid binding proteins, was measured by the Phadebas T_3 U Test (Pharmacia, Uppsala, Sweden). Normal values were 75–115 TBP%.

The free T_4 index was calculated as $T_4 \times T_3\text{-uptake}/100$. The normal range was 67–153 arbitrary units.

The free T_3 index was calculated as $T_3 \times T_3\text{-uptake}/100$. The normal range was 1.2–2.8 arbitrary units.

The free levonorgestrel index (FLI) was calculated as $\text{nmol/l of levonorgestrel} / \text{nmol/l of SHBG capacity} \times 100$.

Cortisol was determined by a radioimmunoassay method (Commercial kit from Farnos Diagnostica, Turku, Finland). Normal serum levels for cortisol with this method between 8.00 and 9.00 AM were: 150–650 nmol/l, and between 3.00 and 4.00 PM: 120–400 nmol/l.

Corticosteroid binding globulin (CBG) was measured by a solid-phase radioimmunoassay described by Robinson et al. (36). Using this method, normal values in healthy, fertile women were 14.5–26.5 mg protein/l. One mg CBG protein was equivalent to a cortisol binding capacity of 22.3 nmol.

The free cortisol index was calculated as $\text{cortisol concentration} / \text{CBG concentration}$.

Oestradiol was determined by a radioimmunoassay described by Edqvist & Johansson and modified by Lindberg et al. (37, 38). Values during normal menstrual cycles are presented in Figure 3.

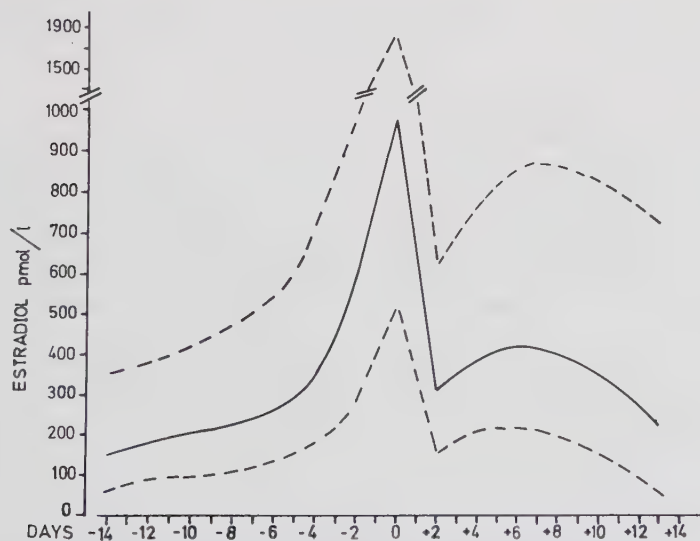


Fig. 3. The mean concentrations and 95% confidence interval of oestradiol in 30 normal menstrual cycles from our laboratory. The days are numbered from the day of the highest oestradiol value.

Progesterone was determined by a radioimmunoassay described by Thorneycroft & Stone and modified as described by Bosu et al. (39, 40). From analyses of normal menstrual cycles at our laboratory, we found that the mean peak progesterone value during the luteal phase was 59.8 nmol/l with 95% confidence limits of 29–90 nmol/l.

FSH and LH were measured by a radioimmunosorbent method described by Wide et al. (41). Values during normal menstrual cycles are shown in Figures 4 and 5. (1 ng/ml = 1 µg/l).

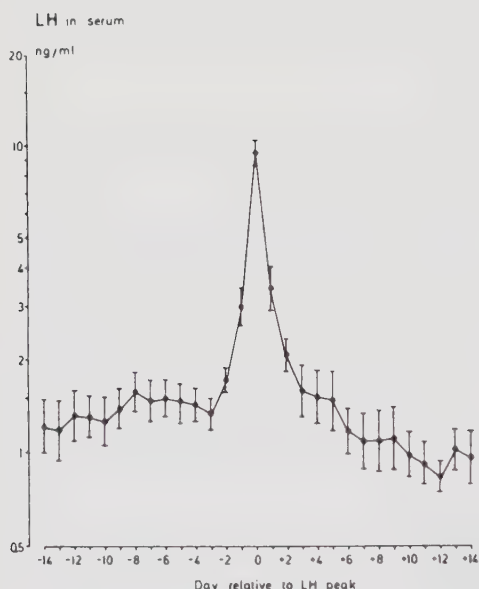


Fig. 4. LH concentrations (Mean±S.E.M.) in serum during 11 menstrual cycles. From: Wide L, Nillius S.J, Gemzell C, Roos P: Radioimmunosorbent Assay of Follicle-Stimulating Hormone and Luteinizing Hormone in Serum and Urine from Men and Women. Acta endocrinol 73: Suppl 174, 1973. Reproduced with kind permission from Periodica, Copenhagen).

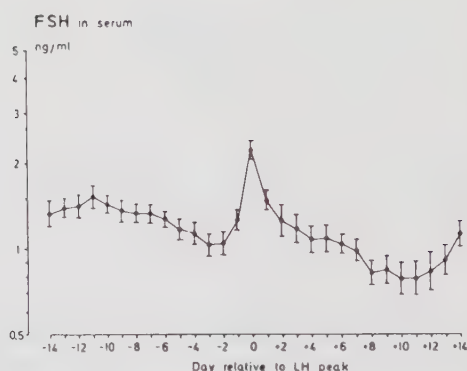


Fig. 5. FSH concentration (Mean±S.E.M.) in serum during 11 menstrual cycles (From Wide L, Nillius S.J, Gemzell C, Roos P: Radioimmunosorbent Assay of Follicle-Stimulating Hormone and Luteinizing Hormone in Serum and Urine from Men and Women. Acta endocrinol 73: Suppl 174, 1973. Reproduced with kind permission from Periodica, Copenhagen).

RESULTS

I. Contraception with NORPLANT^R implants and NORPLANT^R-2 implants (two covered rods). Results from a comparative clinical study in Sweden

Two-hundred-and-forty healthy women, of ages 18 to 40 years, were randomly allocated in a ratio of 2:5 to use of NORPLANT^R implants or NORPLANT^R-2 implants. Through three years of use no pregnancies were recorded among women using NORPLANT^R implants and two pregnancies were noted among those using NORPLANT^R-2 implants, resulting in a cumulative net pregnancy rate of 1.3 ± 0.9 per 100 acceptors (mean $\pm$ SE) by the end of year three. This difference was not statistically significant.

In 431 woman-months of use during year four, four pregnancies occurred among users of NORPLANT^R-2, resulting in a Pearl rate for that period of 11.1 per 100 woman-years. However because of the above-mentioned 2:5 ratio between the enrolled women of the two groups, the observed overall distribution of 0:6 pregnancies between the two methods was not statistically significant.

The predominant reason for terminating the study was bleeding disturbances. During the first year there were significantly more terminations of use due to such problems in the NORPLANT^R group (26.1%), than in the NORPLANT^R-2 group (14.0%). However, during the second year of use, the proportion of women discontinuing for bleeding problems dropped considerably among NORPLANT^R users and during the third year very few women in either group discontinued because of such problems. The one-year continuation rate was for NORPLANT^R users 59.4% and for NORPLANT^R-2 users 77.2%. This difference was statistically significant. The corresponding figures after three years of use were 46.1% and 51.7% respectively (the difference was not statistically significant).

The second most common, though infrequent reason for discontinuation was depression and other mood changes. In both groups a slight increase in weight and a slight decrease in blood pressure and haemoglobin level were noted with time during the study period.

In conclusion, both NORPLANT^R and NORPLANT^R-2 implants are very effective methods for contraception. The efficacy of NORPLANT^R-2 implants, however, was not acceptable during the fourth year of use in this study. The latter system

could, however, become a suitable three-year contraceptive method, possibly with fewer bleeding disturbances than NORPLANT[®] in the first year.

II. Plasma levels of levonorgestrel and “free levonorgestrel index” in women using NORPLANT[®] implants or two covered rods (NORPLANT[®]-2)

Plasma concentrations of levonorgestrel, and oestradiol and the SHBG capacity were studied over a period of four years in 283 healthy women using either NORPLANT[®] implants or two covered rods (NORPLANT[®]-2). The women were randomly allocated to use of either type of implant. Both implant systems have previously been shown to have similar rates of release of levonorgestrel. In both groups the mean plasma level of levonorgestrel decreased throughout the study, and showed no statistically significant differences between the two groups. The reduction was most pronounced during the first nine months of use, for both types of implants. There was a tendency towards a steeper decrease in the plasma level of levonorgestrel in users of the two covered rods. During the study eight women became pregnant. All pregnancies but one occurred after 35 months of implant use and only in women using the covered rods. No significant difference in the mean plasma level of levonorgestrel was found between the women who became pregnant and the rest of the group using the two covered rods (Figs 6 and 7).

The mean plasma level of oestradiol was significantly higher at 12, 24, 36 and 48 months than after one month of implant use, with no significant difference between women using NORPLANT^R or the two covered rods.

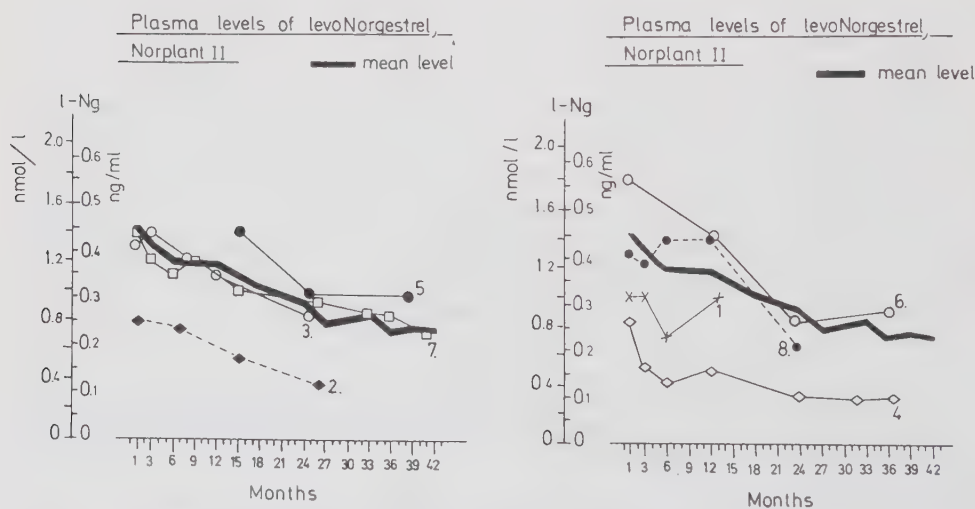


Fig. 6-7. Plasma levels of levonorgestrel in women who became pregnant during use of NORPLANT-2 implants. The levels shown, represent values obtained prior to, but not during, pregnancy. The figures refer to data mentioned in paper II. For comparison the mean plasma concentration of levonorgestrel for users of NORPLANT-2 is shown.

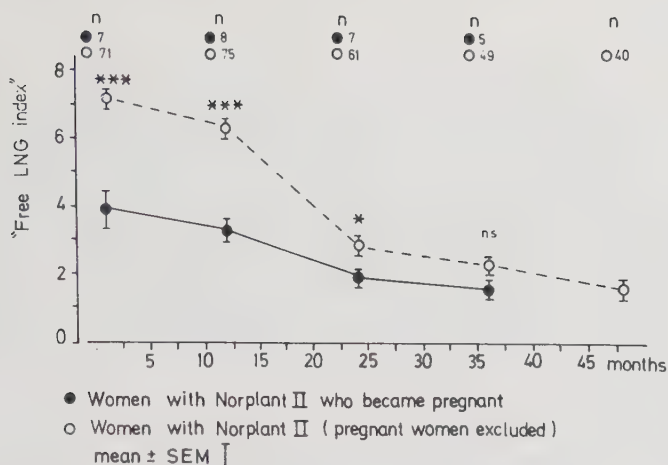


Fig. 8. The “free levonorgestrel index” (FLI) in women who became pregnant (filled circles) during use of NORPLANT-2 compared to the FLI in those who did not become pregnant (open circles) during use of NORPLANT-2. * = $p < 0.05$, *** = $p < 0.001$.

The SHBG capacity was somewhat higher throughout the study in the latter women than in the users of NORPLANT^R. Among the women who used two covered rods there was a tendency towards an increase in the mean SHBG capacity after 24 months of use, which was not seen in the users of NORPLANT^R.

As levonorgestrel is to a great extent bound to SHBG, and in the bound form is not biologically active, a “free levonorgestrel index” (FLI) was calculated as the ratio between levonorgestrel and SHBG. This index was significantly lower after 1, 12 and 48 months of use in users of two covered rods than in women who used NORPLANT^R implants. Women who became pregnant had a significantly lower FLI than had the rest of the group (Fig 8). It is postulated that the difference in FLI between the users of the two implant systems reflects differences in the release rate, the covered rods possibly having a lower release rate of levonorgestrel than NORPLANT^R throughout the observation period. It is concluded that the FLI is a better parameter than the levonorgestrel plasma level for indicating implant function and for discriminating women at risk of becoming pregnant.

III. Androgen levels in women using NORPLANT^R implants

SHBG capacity, plasma concentrations of total testosterone, free testosterone, androstenedione (A4) and levonorgestrel were studied in 17 women before and during the first 12 months of use of NORPLANT^R-2. There was a highly significant decrease in SHBG capacity during treatment. The total testosterone and A4 levels also decreased significantly. Free testosterone remained unchanged. Diurnal varia-

tions were found to occur for A4 and total and free testosterone, but not for SHBG or levonorgestrel.

In addition, the plasma concentrations of testosterone, free testosterone and levonorgestrel and the SHBG capacity were measured in two groups of women participating in a comparative clinical trial of NORPLANT^R versus NORPLANT^R-2 implants, one of which group, at the one-year follow up, denied and the other claimed to have noticed increased facial acne during treatment. There was no difference regarding SHBG capacity, total testosterone, free testosterone or levonorgestrel between the groups of women with and without increased facial acne. However, the women in the group noticing increased acne during treatment, reported significantly more often that they had had acne before treatment, than the women who did not notice increased acne.

It is concluded that neither the use of NORPLANT^R nor of NORPLANT^R-2 implants results in increasing plasma levels of androgens.

IV. Aspects of thyroid function during use of NORPLANT^R implants

Plasma T₄, T₃ and TSH, and T₃-uptake were measured in 18 women using NORPLANT^R implants or NORPLANT^R-2 implants for six months. The free T₄ index and free T₃ index were also calculated.

T₄ decreased and T₃-uptake increased, indicating a lower level of thyroid binding proteins during treatment. The T₃ level did not change. The free T₄ index remained unchanged, indicating that the free concentration of thyroxin was unaltered. All women were euthyroid and TSH remained unchanged.

It is concluded that neither the use of NORPLANT^R nor NORPLANT^R-2 implants results in a change in thyroid function.

V. Plasma levels of cortisol and corticosteroid binding globulin during use of NORPLANT^R-2 implants

Plasma levels of cortisol and CBG were studied during a period of one year in 11 healthy women using NORPLANT^R-2 implants. A significant diurnal variation of the plasma cortisol level was found during the study. No significant change in this level was found as compared with the pre-treatment value. The plasma concentration of CBG showed no diurnal variation, but decreased significantly during use of the implants. This was most probably due to a direct effect of the levonorgestrel, as mean plasma concentration of oestradiol remained at the pre-treatment level, except after 6 months when the value was significantly lower than the pre-treatment value (Fig 9). A "free cortisol index" calculated as the ratio between the plasma levels of cortisol and CBG, did not change during treatment compared with the pre-treatment level.

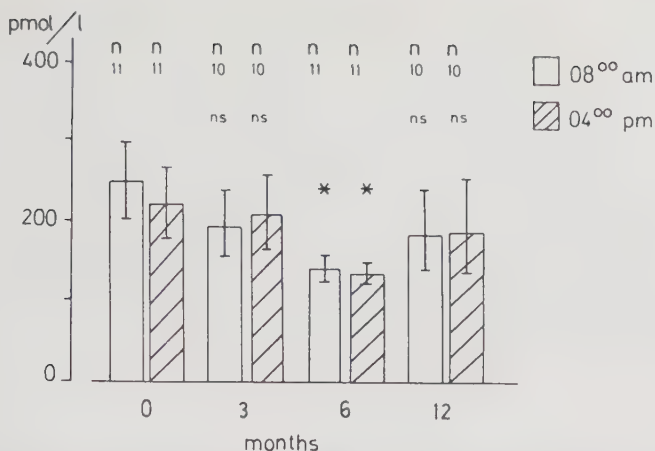


Fig. 9. Mean $\pm$ SE plasma concentration of oestradiol (pmol/l) before and during use of NORPLANT-2 implants. (* = $p < 0.05$).

It is concluded that although the CBG level was reduced, there was no significant change in the cortisol pattern during use of the implants.

VI. Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with NORPLANT^R implants

A 26-year-old woman, treated with phenytoin for ten years because of epilepsy, had NORPLANT^R subdermal implants inserted after a legal abortion. She became pregnant again after nine months of NORPLANT^R use, and had an abortion. One month after the abortion her plasma levonorgestrel levels were followed for one month during phenytoin treatment and then later for one month after discontinuation of phenytoin. During phenytoin treatment, her plasma levonorgestrel level was markedly below the levels found in healthy women with NORPLANT^R. There was a pronounced, statistically significant increase in the plasma levonorgestrel level after discontinuation of phenytoin. The SHBG capacity was markedly above that found in normal healthy women during treatment with phenytoin and decreased significantly after cessation of phenytoin therapy. The "free levonorgestrel index" (FLI) increased after discontinuation of phenytoin. The effects of phenytoin on the pharmacokinetics of levonorgestrel were reflected by the effects on the menstrual cycle. During phenytoin treatment, the woman had regular ovulatory menstrual cycles, but after cessation of this treatment, her cycles became irregular and during the one-month study period no signs of ovulation were found.

It is concluded that treatment with phenytoin during use of NORPLANT^R subdermal implants increases the metabolism of levonorgestrel to an extent at which the contraceptive efficacy is endangered.

VII. Ovarian function during use of subdermal implants releasing low doses of levonorgestrel

Ovarian function was studied by use of ultrasonography and hormonal measurements during one menstrual cycle in 15 women, who had used NORPLANT[®]-2 since more than three years. All the women had reported regular menstrual periods during the last year preceding the study. The dose delivered from the rods has not yet been determined, but a large clinical study has recently shown a pronounced increase in the pregnancy rate after year three, suggesting that the delivered dose at that time is close to the margin of contraceptive efficacy.

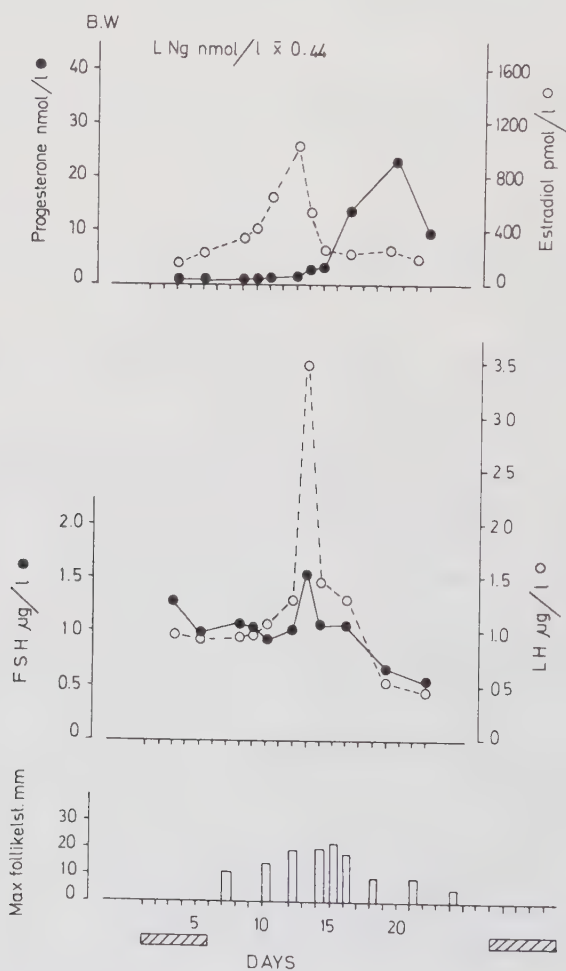


Fig. 10. Plasma concentrations of estradiol, progesterone, FSH and LH during a menstrual cycle in one woman who had used NORPLANT-2 implants for more than three years. Ultrasound determinations of follicle diameter shows a normal follicular development and rupture. Days are numbered from the first day of menstrual bleeding.

Six of the 15 women had ultrasonographic and hormonal signs of ovulation (Figs 10 and 11), whereas six showed no signs of ovulation (Figs 12 and 13) and three had signs of luteinization of an unruptured follicle (Fig 14). The mean maximum follicular diameter in the ovulatory group was 20.8 ± 5.3 mm (mean $\pm$ SD). In the women who did not ovulate the mean maximum follicular diameter was 33.5 ± 6.6 mm (mean $\pm$ SD). In the women who ovulated, distinct LH peaks were found, but the peak LH values were always lower than are usually seen in fertile women. In the women who developed luteinization of an unruptured follicle, and in those who did not ovulate, LH increased in response to the increase in oestradiol, but there were no distinct LH peaks. The endometrial thickness was assessed with ultrasound. The endometrium was generally thinner (1.5 to 3.7 mm) than in untreated fertile women (Fig 15).

It is concluded that although the dose of levonorgestrel delivered from the two covered rods is very low and close to the margin of contraceptive efficacy, it exerts an effect on follicular development in the majority of women, presumably via effects on the gonadotrophin secretion. Despite the low dose, it also seems to have an effect on the endometrium, possibly contributing to the contraceptive efficacy.

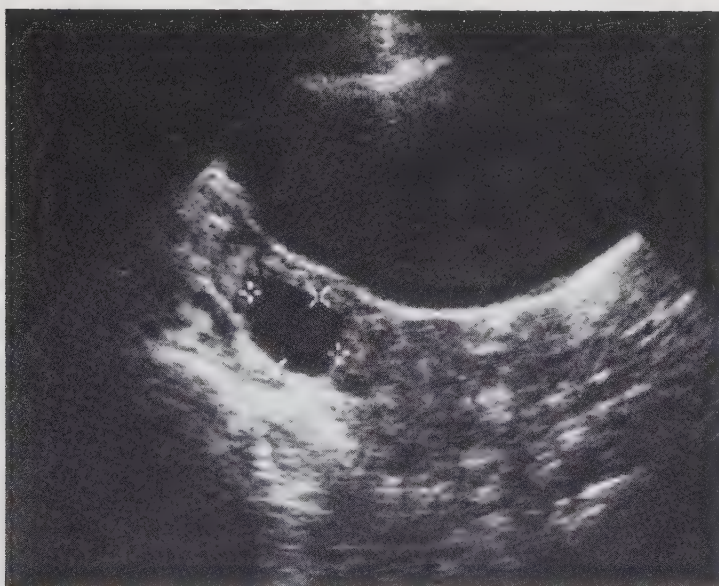


Fig. 11. A typical ultrasound representation of a preovulatory follicle, which later ruptured. The woman had used NORPLANT-2 implants since more than three years.

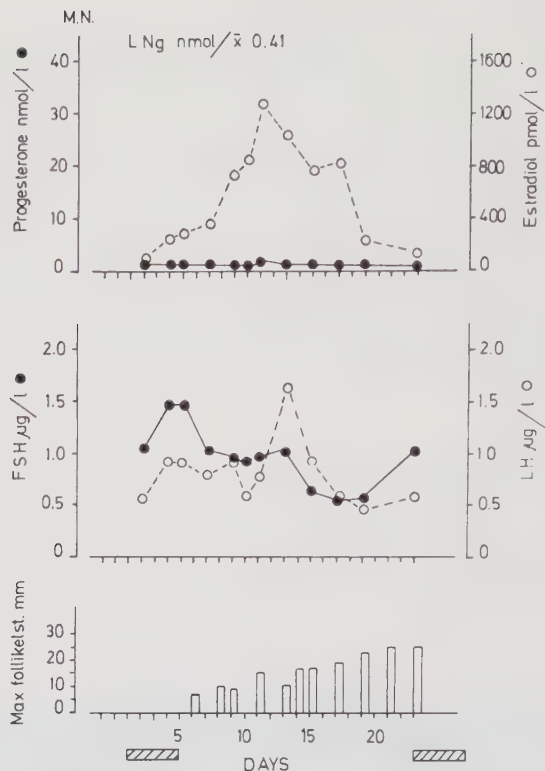


Fig. 12. Plasma concentrations of estradiol, progesterone, FSH and LH during a menstrual cycle in one woman who had used NORPLANT-2 since more than three years. Ultrasound determination of follicle diameter shows the development of a follicle but no follicular rupture. Days are numbered from the first day of menstrual bleeding.

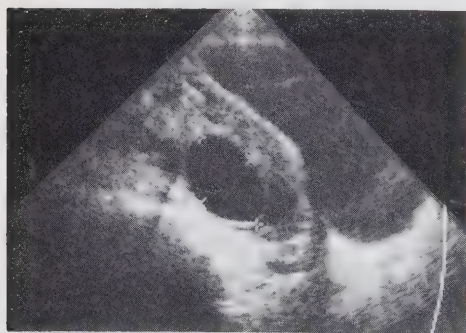


Fig. 13. A typical ultrasound representation of an unruptured follicle from an anovulatory cycle in a woman who had used NORPLANT-2 for more than three years. The picture is taken on cycle day 25. Maximum diameter is 34.9 mm.

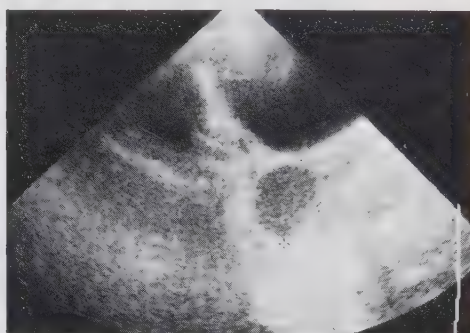


Fig. 14. A typical ultrasound representation of a luteinized unruptured follicle. The woman had used NORPLANT-2 since more than three years. The picture is taken on cycle day 23.

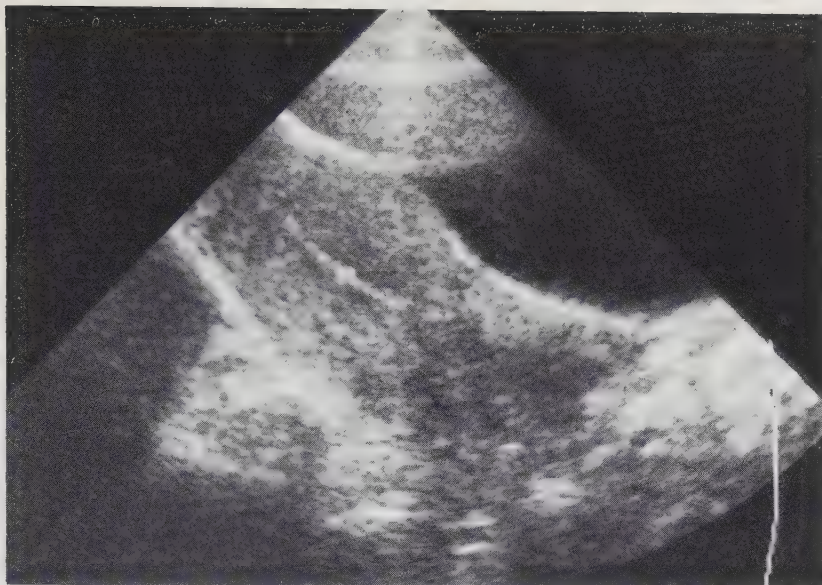


Fig. 15. A typical representation of the endometrium by ultrasound of a woman who had used NORPLANT-2 since more than three years. The endometrial thickness in this woman was 12 mm.

DISCUSSION

Both implant systems were highly effective during the first three years of use. The four pregnancies in year four among NORPLANT[®]-2 users in the randomized comparative study may indicate that the efficacy of this regimen diminishes after three years. Further investigations are needed, however, to establish whether NORPLANT[®]-2 implants in general are highly effective for only three years, or whether the pregnancy rate during the fourth year observed in the present study was due to a specific problem with the currently used covered rods or to a chance variation (I).

We found no significant differences in plasma levels of levonorgestrel between users of the two systems of implants. This seemed to support the report that the release rate of levonorgestrel was the same for both types of implants (26). The plasma concentrations of levonorgestrel in both groups of women decreased throughout the observation period of 48 months, and the decrease was most pronounced during the

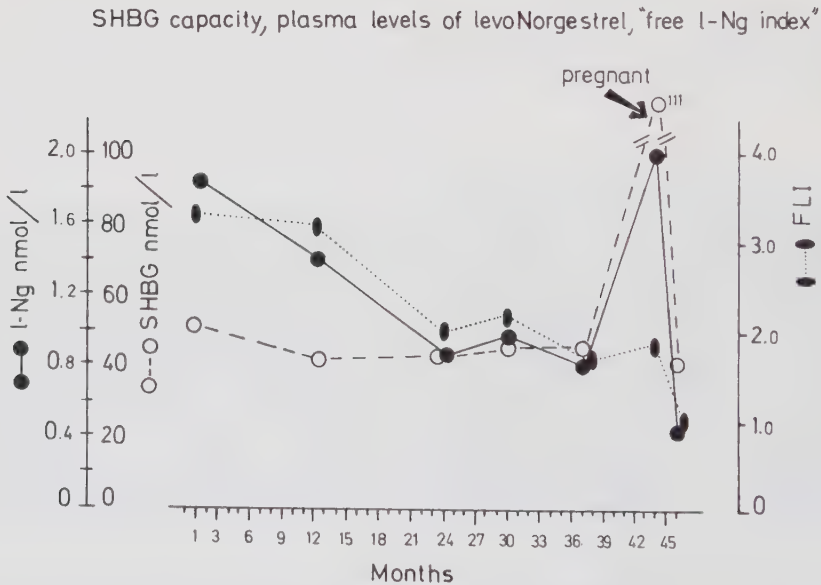


Fig. 16. Plasma concentration of levonorgestrel, SHBG capacity and "free levonorgestrel index" (FLI) in a woman using NORPLANT-2 implants before, during and after a pregnancy which was terminated with an abortion. The figure illustrates the relationship between SHBG capacity and levonorgestrel plasma concentration.

first nine months. The slope of the curve for plasma levonorgestrel levels in women using NORPLANT^R-2 was steeper than that for NORPLANT^R, indicating that, if the plasma levels reflect the release rate of levonorgestrel, the release from NORPLANT^R-2 decreases at a faster rate.

Clinically there was a difference in performance between the two systems, in that several women became pregnant when using NORPLANT^R-2 implants but none in the NORPLANT^R group (I, II). The plasma levels of levonorgestrel did not discriminate these women from the rest of the group, as seen in Fig 6 and 7. The same finding was reported by Diaz et al. (42).

After the first year of use, the SHBG capacity increased in users of both types of implants. After two years of use, this capacity continued to rise in users of NORPLANT^R-2, but not in users of NORPLANT^R. In the women who became pregnant the SHBG capacity usually lay within the range normally seen in healthy menstruating women, except for women with overweight, who had lower levels. Levonorgestrel binds with a high affinity to SHBG, and plasma levonorgestrel values vary with SHBG capacity (43, 44, 45). This relationship between the circulating levonorgestrel level and SHBG capacity was clearly demonstrated in one woman who became pregnant while using NORPLANT^R-2. She showed a pronounced increase both in the SHBG capacity and in the plasma concentration of levonorgestrel during pregnancy (Fig 16). In contrast, a marked increase in the levonorgestrel concentration and a concomitant decrease in SHBG capacity were noted in one woman in whom phenytoin treatment was discontinued during the use of NORPLANT^R. In this particular woman the phenytoin treatment had probably enhanced the metabolic degradation rate of levonorgestrel and induced an increase in SHBG capacity (VI). Similar findings were reported by Haukamaa et al and Beastall et al. (46, 47).

Possible reasons for the increase in SHBG capacity observed in women of both implant groups are a) decreasing release of levonorgestrel with time, resulting in a reduced inhibition of SHBG synthesis, and b) increasing oestradiol concentrations in the plasma as a result of restored ovarian function, which in turn could be due to a decrease in levonorgestrel release. The oestradiol levels increased after the first months of use, but there were large interindividual variations, and no significant difference in oestradiol level was found between users of the two types of implants. The SHBG capacity would theoretically be expected to increase during the luteal phase of the menstrual cycle, as a response to the preovulatory oestradiol peak, but very few investigators have found such an increase (48). In a study by Odland et al., with use of the same method for measuring SHBG as in the present studies, no changes in SHBG capacity were observed during the menstrual cycle. Moreover, in gonadotrophin-stimulated cycles, the oestradiol level had to exceed 1,000 pmol/l before an increase in SHBG capacity could be detected (33). The increase in SHBG capacity found in the present study was more probably caused directly by decreasing

plasma concentrations of levonorgestrel, than by increasing concentrations of oestradiol. Recent reports have suggested, however, that the SHBG capacity is not only influenced by oestrogens, androgens and progestogens, but could also be influenced a great deal by somatomedins, and only modulated by sex hormones (49, 50, 51). It has also been reported that the SHBG capacity is increased in hyperthyroidism and decreased in hypothyroidism (52). All women in the present studies were clinically euthyroid.

Whatever the reason for the increasing SHBG capacity, the resulting effect will be that more levonorgestrel will bind to SHBG with high affinity, and in that form not being biologically active (53). Neither the plasma levels of levonorgestrel nor the SHBG capacity showed a clear difference between the two methods, but the calculated FLI differed between the two methods and was significantly lower in users of NORPLANT^R-2 after 1, 12 and 48 months of use. FLI was significantly lower from the beginning of implant use in the women who became pregnant, during use of NORPLANT^R-2 than in those who did not. The most probable reason for these difference in FLI and in the biological effect between the two implant methods is a difference in the rate of release of levonorgestrel. It has previously been reported that during the first year of use, NORPLANT^R has a release rate of 60 to 80 ug/day and NORPLANT^R-2 approximately 50 ug/day (26). The difference in initial release is probably the reason for the lower FLI among users of NORPLANT^R-2 during year one (II).

There is a relationship between the dose of levonorgestrel from implants and the plasma concentration of levonorgestrel, but as demonstrated by Robertson, an increase in dose by 100% does not result in a doubling of the plasma concentration of levonorgestrel (24). From the results discussed above it is clear that the plasma level

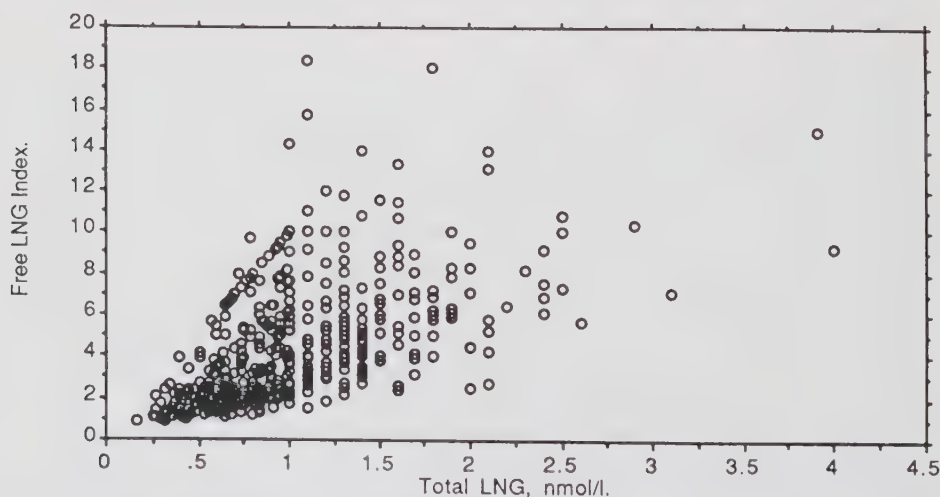


Fig. 17. Correlation between "free levonorgestrel index" (FLI) and plasma concentration of levonorgestrel.

of levonorgestrel does not reflect the release rate and is not a very sensitive factor for the prediction of risk of pregnancy. Even if the FLI does not exactly reflect the amount of free levonorgestrel in plasma, since it does not take other steroids bound by SHBG and other binding proteins into account, it offers a simple measure of biologically active levonorgestrel and gives a better picture of levonorgestrel effects than plasma levels of this steroid. The correlation between FLI and plasma levels of levonorgestrel is shown in Fig. 17. For FLI below 2 which might indicate an increased risk of becoming pregnant, plasma levels of levonorgestrel sometimes exceeded 1.0 nmol/l.

The FLI, however, is not always predictive of a high risk of pregnancy, as is evident from the results of study VII. Although all the women had a low FLI, only 40 per cent ovulated. On the other hand, a woman with a high FLI will probably run quite a low risk of becoming pregnant (II, VII).

The pregnancy rate was one of two biological variables that differed between the two implant systems, the other being the bleeding pattern.

The difference in continuation rates between users of the two implant systems during the first year of use was mainly referable to differences in termination for bleeding problems. This again could indicate that the two systems have different release rates of levonorgestrel, users of NORPLANT[®] implants starting with a slightly higher dose, resulting in more pronounced disturbance of the ovulatory function, which in turn could result in more bleeding irregularities. This was in fact demonstrated in the woman who during phenytoin treatment had a low FLI and regular menstrual periods, and after discontinuation of phenytoin had a high FLI and menstrual irregularities (VI). The very low FLI in women who became pregnant in the present studies and the finding by Diaz et al. of regular menstrual bleeding at least six months before pregnancy in all women who became pregnant during use of NORPLANT[®] implants are further indications of the association between low release of levonorgestrel, regular menstrual periods and an increased risk of pregnancy (42). Although all the women studied with ultrasound had a low FLI, and normal menstrual periods, we did not find convincing signs of ovulation in more than 40 per cent, indicating that there are great interindividual variations in the response to a particular dose of levonorgestrel (VII). There is probably a rather narrow dose range for levonorgestrel within which it has a minimum of effects on the ovarian cycle and the menstrual pattern and still a high contraceptive efficacy. From the present studies and from several other reports in the literature it seems as if the levonorgestrel dose from NORPLANT[®], especially after 12–18 months of use, falls well within this dose range (8, 54, I, II, VII).

A higher levonorgestrel dose and more pronounced disturbances of the ovarian cycle, was not, however, the only probable reason for the higher discontinuation rate for bleeding problems among users of NORPLANT[®] during the first year. The

presence of a larger proportion of former barrier method users in the NORPLANT^R group contributed to the initial significant differences in the termination rates for bleeding problems. Women who had used barrier methods had significantly higher termination rates for bleeding problems than other women and in the NORPLANT^R group there were relatively more of these women. It may be postulated that former barrier method users had less experience in the kind of bleeding problems that not infrequently occur in users of hormonal methods and IUDs and therefore had low tolerance towards such problems (I).

The types of bleeding disturbances reported were frequent irregular bleeding and prolonged bleeding (I). An increased frequency of spotting was also reported. The mechanism underlying the irregularity is probably oestradiol peaks of invariable duration and frequency (22). The mechanism behind prolonged bleeding and spotting might be that progestogens in some instances induce the development of superficial thin-walled sinusoids in the endometrium (55, 56).

The progestogens induce a variety of changes in the endometrium, most of which are poorly understood. One of the changes noted is that progestogens suppress oestrogen receptor concentration in endometrial tissue (55). It has been claimed, but not demonstrated in any comparative study, that treatment of bleeding disturbances could be accomplished by the administration of oestrogens. The duration of such therapy is probably more important than the dosage, as it requires some time to stimulate new oestrogen receptor formation before a clinically useful effect on the endometrium can be seen. If oestrogen does have the beneficial effect which is sometimes claimed, it presumably produces this through a proliferative effect on the endometrium which allows surface growth over superficial thin walled sinusoids (55). Repeated oestrogen therapy during the use of NORPLANT^R implants is, however, not always appropriate, since, most women using this method have chosen it because it is an oestrogen-free method, or that because of smoking, age or side effects they are not suitable for oestrogen therapy.

The best way of handling bleeding disturbances is to give good counselling before starting the method, including information about what bleeding patterns to expect during the use of the implants. Apart from direct effects of levonorgestrel on the endometrium, other possible causes of bleeding disturbances such as cervical neoplasia and infections must never be overlooked (57).

A number of plasma proteins such as SHBG, TBP — measured as T₃-uptake test and CBG were all reduced during use of the levonorgestrel-releasing implants. Several investigators have shown that the concentration of SHBG is increased by oestrogens and decreased by androgens (58, 59, 60, 61) Levonorgestrel binds with high affinity to SHBG, and our method of analysis is a displacement-saturation process with tritiated dihydrotestosterone (³DHT). Theoretically, binding of levonorgestrel to SHBG could disturb this analysis, but it has been found that the binding

affinity of DHT to SHBG is 12.5 times greater than that of levonorgestrel, and DHT is added in great excess in the analysis (own unpublished results, 33).

Concomitantly with the reduction in SHBG capacity, a decrease in the plasma concentration of total testosterone was noted (III). The reduced SHBG capacity could be expected to result in an increase in the free fraction of testosterone. However, this is probably compensated by an increased metabolic clearance rate of testosterone, which could be the explanation for unchanged levels of free testosterone (62, III).

In the clinical study 20–25 per cent of the women using NORPLANT^R or NORPLANT^R-2 reported increased acne and about two per cent discontinued use of the implants because of acne during the first year. No differences in androgens or SHBG capacity were found, however, between women with and women without acne (III). It was therefore postulated that acne in this study was rather a result of a direct effect of levonorgestrel on the skin in sensitive persons than an effect mediated via endogenous androgen changes. Similar findings have been reported by others (63, 64).

TBG is the most important thyroxine binding protein assayed by the T₃-uptake test. It has previously been shown that TBG is increased by oestrogens (65). The endogenous oestrogen concentrations in users of NORPLANT^R implants during the first year of use have been reported to be in the range usually found during the early to mid-follicular phase of the menstrual cycle (22). As the mean oestrogen concentration is not significantly lower during use of levonorgestrel-releasing implants than in normal cycles, the most probable explanation for the observed decrease in thyroxine binding proteins is therefore a direct effect of levonorgestrel on the levels of TBG.

The plasma T₄ concentration decreased concomitantly with the reduction of TBP. However, the TSH level was unchanged, indicating that the thyroid function was unaltered (IV).

The decrease in CBG is probably also a direct effect of levonorgestrel. A tendency towards lower levels of CBG has also been found during use of levonorgestrel by Ruokonen and Käär (66, 67).

There was a concomitant tendency towards decreasing concentrations of cortisol in the plasma, though not significant. The great interindividual variations in cortisol levels could be the reason why this decrease was not being statistically significant. Some investigators have reported reduced levels of cortisol during use of NORPLANT^R implants (16, 68, 69), whereas others have reported that cortisol levels in users of NORPLANT^R did not differ from those using an IUD (70, 71). Cortisol levels normally have large interindividual variations, and there is also a diurnal variation, (72, 73). The clinical significance of the reported findings are probably of

little, if any clinical significance, since the observed changes were always well within normal limits. The observed insignificant decrease in cortisol levels might be a result of the decreased concentration of CBG (V).

According to Weiner et al. and Moore et al., during the first year of NORPLANT^R use, most women are anovulatory (22, 74). The frequency of presumed ovulatory cycles increases with the duration of implant use, but the contraceptive efficacy of NORPLANT^R remains high throughout a period of five years (75, 76). The exact mechanism of the contraceptive effect during the later period of NORPLANT^R use is therefore not completely understood. In the present study the ovarian function was studied in detail in women who apparently had normal cycles as judged by their menstrual pattern. Despite this "normality", abnormal follicular development was found in the majority of women studied and all had low LH peak levels (VII). Oestradiol peaks were found in the absence of ovulation, most probably due to the development of ovarian follicles producing oestradiol, which in several cases developed into small follicular cysts (VII). The frequency of functional cysts in users of NORPLANT^R has been very little studied. Ovarian enlargement has been reported to occur in around ten per cent of women with NORPLANT^R during the first three years of use, presumably in many cases as a result of functional cysts (16, 77). The low LH peaks found are probably due to a disturbed feed-back mechanism of oestradiol on the hypothalamus, presumably by change of the normal pulse frequency and/or amplitude of LH. Luteal function is dependent on LH pulsatility, and again, a possible explanation for the lower progesterone levels in spite of a follicular rupture might be that the LH pulse frequency is disturbed and thereby does not stimulate the corpus luteum adequately (78). Other authors have also speculated on a direct disturbance of the progesterone synthesis in the corpus luteum by administration of progestogens, as an explanation for the lower plasma concentration of progesterone (79).

In apparently ovulatory cycles, minimal hormonal changes probably add to the contraceptive effect. Another contraceptive effect is exerted through progestogen action on the endometrium (VII). A third contraceptive mechanism, not examined in this study, is the effects of the progestogens on cervical mucus, making it thick and impermeable to sperm (80).

GENERAL SUMMARY

1. The contraceptive efficacy of NORPLANT[®] implants was excellent throughout the four years of observation and that of NORPLANT[®]-2 implants was very good during the first three years of use. During the fourth year of use, the contraceptive efficacy of NORPLANT[®]-2 implants was not acceptable.
2. The most common side effect experienced by users of both types of implants was bleeding disturbances such as irregular bleeding and periods of prolonged bleeding. The frequency of such disturbances decreased considerably after the first year of use.
3. No serious side effects were noted. Side effects other than bleeding disturbances were mild and infrequent.
4. The plasma concentrations of levonorgestrel decreased throughout the study period. The reduction was most pronounced during the first nine months. The decrease was steeper for NORPLANT[®]-2 than for NORPLANT[®]. There was no statistically significant difference in plasma concentrations of levonorgestrel between users of the two types of implants.
5. The plasma concentrations of levonorgestrel in women who became pregnant did not differ from those in women who did not become pregnant.
6. Women who became pregnant had a higher SHBG capacity than those who did not. They also had a significantly lower "free levonorgestrel index" than women who did not become pregnant.
7. It is suggested that NORPLANT[®]-2 implants have a lower release rate of levonorgestrel than NORPLANT[®] implants, as reflected by a higher pregnancy rate, a slightly higher SHBG capacity and a lower "free levonorgestrel index".
8. SHBG, TBP and CBG decreased during use of the implants.
9. The plasma concentrations of testosterone and androstenedione decreased during implant use. The free testosterone concentration remained unchanged.

10. Women who noticed increased acne during treatment did not differ from the rest of the women with respect to the plasma concentrations of levonorgestrel, testosterone or free testosterone or the SHBG capacity. Women who reported acne before insertion of the implants more often experienced increased acne during their use than those who did not report acne before insertion.
11. Thyroid function did not change during use of the implants.
12. The plasma cortisol concentration remained unchanged during use of the implants.
13. Treatment with phenytoin substantially decreased the contraceptive efficacy by increasing the levonorgestrel metabolism, and the SHBG capacity.
14. Despite regular menstruations in a group of women who had used NOR-PLANT[®]-2 implants for more than three years, 40 per cent showed anovulation, 20 per cent unruptured luteinized follicles and 40 per cent apparent ovulations.

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CONTRACEPTION WITH NORPLANT[®] IMPLANTS AND NORPLANT[®]-2 IMPLANTS (TWO COVERED RODS) Clinical results from a comparative study in Sweden

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